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EUROPEAN PATENT OFFICE

PCT DIVISION

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GERMANY

VIA FACSIMILE
(confirmation by COURIER)

To the attention of Mr. W. Zeslawski,
Authorized Officer

Re : UNIVERSITE DE MONTREAL et al
International patent application
No. PCT/CA03/00487 filed on April 3rd, 2003
Our ref.: 000711-0024

Dear Sir:

This is in response to the Written Opinion mailed on January 16, 2004.

A- In this Written Opinion, the Examiner has confirmed having taken into account the voluntary amendment submitted by the Applicant on November 3, 2003.

However, in point V detailed on the separate sheet attached to the Written Opinion, the Examiner has objected to the amendments made on page 1, line 27; page 2, line 18; page 7, line 16 and page 14, line 28, as being allegedly not supported by the original description.

With respect to the replacement of the word "hydrophobicity" by --insolubility-- on page 1, line 27, the Applicant submits that any one skilled in the art would know that the affirmation made by error that compounds like PLA, PLGA, PCL have a high hydrophobicity is not exact. Polylactic and polyglucolic acid are obviously not hydrophobic. These compounds are polar compounds but not soluble and more precisely not swellable in an aqueous medium. Accordingly, it has been found that the word --insolubility-- would be descriptive of the actual problem encountered with this kind of compounds.

With respect to the replacement of the word "polymerization" by --polycondensation-- on page 2, line 18 of the description, it is submitted again that any one skilled in the art would know that the kind of reaction referred to in the preceding part of the description dealing with the preparation of PLA based polymers is not a polymerisation reaction but a polycondensation reaction.

With respect to the amendment made on page 7, line 6, the Applicant submits that the expression "C1-C4" has been replaced by --C₁-C₄-- for the purpose of clarification. The numbers 1 and 4 used to identify the number of carbon atoms have been converted from a capital size to a smaller size. This does not amount to an introduction of new matter.

With respect to the replacement of the expression "palmitoleic acid" by --palmitic or oleic acid-- on page 14, line 29 of the description, the Examiner is probably right. Thus, it is respectfully requested that page 14 that was submitted on November 3, 2003, be disregarded and original page 14 be reinserted into the description.

B- In point V in the separate sheet attached to the Written Opinion, the Examiner is also objected to the dependency of claim 6 that would be incorrect.

In response to this objection, the Examiner will find enclosed an amended page 17 to be substituted for page 17 presently on file. As will be noticed, the dependency of claim 7 has been amended so that this claim be dependent on any one of claims 1 to 5 instead of claim 7.

C- Last of all, in point V of the Written Opinion, the Examiner has objected to the novelty and inventiveness of some of the claims presently on file in view of international laid-open patent application No. WO 03/000766A1 (document D1).

(a) As already mentioned by the Applicant in the letter sent by fax to the EPO on November 3, 2003, document D1 is classified in category X and P in the International Search Report, inasmuch as it was actually published after the priority date of the present application. For this reason, this document can be cited against the present application:

- a) only to support a rejection for lack of novelty and (not for the lack of inventiveness); and
- b) only in the countries in which this international patent application would be validated.

From information data that the Applicant got on some *web sites* that were visited for this purpose, it seems that national entry of document D1 has not been completed anywhere. As a matter of fact, it seems that the only corresponding application that was published since that time is the corresponding U.S. patent application from which derives document D1, which was published on March 13, 2003 under No. US 2003/050426 A1.

Accordingly, it is believed that this document should not be considered as relevant prior art, except in the United States.

(b) In addition to the above, it is submitted again that the content of document D1 is well known to the Applicant.

In this connection, it is worth mentioning that this inventor/applicant named in Document D1, namely Mr. Venkatram Prasad SHASTRI, was also named as co-inventor when the U.S. application serial No. 60/369,808, the priority of which has been claimed herein, was filed on April 5, 2002.

The invention forming the subject matter of the present application is directed to a very specific family of polymers that could be considered as encompassed in part within some of very broad definitions given in Document D1 (see for example claim 27), but that are not otherwise disclosed and/or exemplified in the same application.

More specifically, the present application is directed to a very specific family of functionalizable polymers of very specific formula (see claim 1 of the present application). These polymers are prepared by a very simple yet efficient process (see claim 8) comprising two basic steps plus an optional third step, which are easy to carry out with high yields. More precisely, the process according to the present invention comprises the steps of:

- a) reacting a cyclic ester or diester monomer or cyclic amide or diamide monomer A with an epoxide of formula III (see claim 8) in the presence of a catalyst;
- b) subjecting the polymer obtained in step a) to an oxidation to convert the $-\text{CH}=\text{CH}_2$ group into corresponding $\text{CH}_2\text{CH}_2\text{OH}$ groups; and
- c) optionally subjecting the polymer obtained in step b) to another oxidation with a Jones mixture to convert the $-\text{CH}_2\text{CH}_2\text{OH}$ group into corresponding carboxylic groups $-\text{CH}_2\text{COOH}$.

The oxidation steps b) and/or c) of the above process can be carried out with hydrogen peroxide. However, in accordance with a particularly preferred embodiment of the invention, these steps are preferably carried out under mild oxidation conditions. For example, such oxidation can be carried out hydroboration at low temperature (see claims 10 and 11).

Once the $-\text{CH}=\text{CH}_2$ groups have been converted into corresponding $-\text{CH}_2\text{CH}_2\text{OH}$ groups, the polymer exhibits several grafting possibilities. As aforesaid, the above-mentioned $-\text{CH}_2\text{CH}_2\text{OH}$ groups can further be oxidized into corresponding $-\text{CH}_2\text{COOH}$ groups, thereby allowing further grafting possibilities.

As aforesaid, Document D1 discloses a very broad family of polymers prepared from hydroxy acid monomers including particular cyclic ester monomers such as lactones or dioxanones (see paragraph 0096) and from monomers provided with an epoxy function (hereinafter called "epoxides").

The whole description of this Document D1 insists on the fact that the epoxides that are already functionalized. More specifically, this description and the few examples given therein make reference to epoxides that have already been functionalized before being copolymerized with cyclic esters. It is only at a few places, but without any concrete examples and/or further description, that reference is made to the fact that the epoxides could be functionalized after having been polymerized with cyclic esters (see paragraphs 0043, 0036, 0040, 0082 and 0095 and claim 27).

In the description of Document D1, reference is also made to the kind of groups that can be used for the functionalization (see for example paragraphs 0069 and 0078). A very broad reference is also made therein made to the fact that one of the functionalizable groups could actually be an unsaturation (see paragraph 0070 and claim 30). However, once again, no concrete examples and/or further description are given.

Thus, Document D1 encompasses within its very broad disclosure, at least in part the first step of the process according to the present invention, in terms of its starting compounds and type of reaction to be carried out.

The very broad description of Document D1 could also be considered as encompassing, at least in part, the second step of the process according to the present invention, inasmuch as mention is made therein to the fact that the functionalizable group of the epoxy monomer can actually be an unsaturation.

However, nowhere in this document, there is disclosed or suggested that this second step is and could actually be an oxidation step.

In this connection, it is submitted that it was not obvious at all when the present invention was made that one could proceed to the oxidation of an unsaturation at one end of an epoxide after this epoxide has been polymerized with an hydroxy acid monomer, without interfering with the ester links of the polymer.

The present invention is actually based of the discovery made after numerous research and experiments, that there is no actually no interference between the ester links or the polymer obtained in the first step of the process according to the invention when this polymer is substantively subjected to an oxidation in order to convert the unsaturation of the epoxide into a $-CH_2CH_2OH$ group.

In addition to the above, the Applicant notes that, in Document D1, a very broad reference is made to potential uses of the compounds that are prepared as disclosed therein. The main advantage in all cases is that the obtained polymers are actually "degradable" (see in particular paragraph 0037).

Amongst the potential uses of these polymers, reference is made to the preparation of particulate and/or capsules in which an active principle can be dispersed or encapsulated in order to obtain an *in vivo* controlled release (see paragraph 00121 and following). However, there is no disclosure or suggestion in this international patent application that the obtained polymers could be grafted to ligands, lipids, peptides, etc..., as is disclosed, exemplified and claimed in the present application (see claim 13). In other words, Document D1 does not make specific reference to the preparation of active vectors. No reference is also made therein to the fact that the particulate of capsules that are obtained may be of a size lower than $1\ \mu$.

(c) As aforesaid, the present invention is "restricted" to very specific amide polymers, their preparation and their uses, which could be considered as broadly disclosed in Document D1 but are not actually disclosed and/or exemplified therein.

It is the Applicant's contention that, almost everywhere throughout the word, it is well settled in Law that any new chemical compound that has been prepared for the very first time and has proved to be actually useful, should be considered as patentable.

In this connection, it is submitted that in chemistry, and more particularly in organic chemistry, most of the new chemical compounds produced today are homologs or analogs of other well known compounds. It is also submitted that most of the processes presently used are actually well known processes that have never been used for preparing the very specific compounds of interest. In all cases, the preparation of a new compound and the discovery of this new compound may be useful may nevertheless be considered as an invention, since, in most cases, it can be held that no "prediction" is possible in chemistry.

From a practical standpoint, any chemical compound could be considered as known *per se* because, in theory, a competent chemist could write a list of all possible chemical compounds that might be brought into existence. However, this theoretical possibility does not prevent the new chemical compound with a given utility from being an invention. Such an invention actually qualifies as a selection, and the patentability of such an invention of selection is recognized almost every where.

In other words, it is believed that inventors who discover a new chemical compound and are in a position to prove that this compound has been prepared and tested with success for a very specific purpose, should actually be entitled to a patent. In this connection, it is believed that it is immaterial that other chemists may have, at any time before, simply written the formula or broadly disclosed it and such could be done without having actually prepared any compound.

Under the present circumstances, it is hereby submitted that the functionalizable polymers and their very specific uses as presently claimed also should be held patentable, since the polymers according to the invention as recited in claim 1 and their use are new. Compounds encompassed within the formula given in claim 1 have actually been prepared and have proved to be useful. The fact these polymers according to the invention are similar to compounds belonging to a very broad class of compounds like the one disclosed in Document D1, does not make them necessarily unpatentable.

(d) In any event, it is believed that more argumentation on this particular issue is not necessary since, as aforesaid, Document D1 was published after the priority date of the present application, and has apparently not been validated in Europe and in any other designated countries, except the USA.

Accordingly, this document is not citable as relevant prior art, except in the USA.

Thus, it is believed that all the claims presently on file should be considered as new and inventive.

For the above mentioned reasons, favourable reconsideration of the Examiner's opinion as expressed in the Written Opinion mailed on January 16, 2004 is respectfully solicited.

Yours very truly

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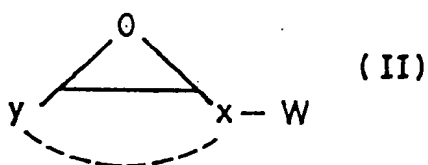
Thierry Orlhac

TO/fm

4. The functionalizable polymer of formula I as claimed in claim 3, wherein the monomer A is selected from the group consisting of caprolactone, glycolide, dilactide and glycolic lactide.

5. The functionalizable polymer of formula I as claimed in claim 1 or 2, wherein Z is -NH- and the monomer A is selected from the group consisting of lactams and dilactams.

6. The functionalizable polymer of formula I as claimed in any one of claims 1 to 5, wherein the monomer B is selected from the group consisting of the epoxides of formula II:



wherein:

X is a non-functional chain optionally containing one or more heteroatoms but no ester or amide link;

W is -CH₂CH₂OH or -CH₂COOH; and

Y is H, alkyl or phenyl;

X and Y being optionally linked to each other as shown in dotted lines.

7. The functionalizable polymer of formula I as claimed in any one of claims 1 to 5, wherein the monomer B consists of alkyl glycidyl ether.

8. A process for preparing a functionalizable polymer of formula I as defined in any one of claims 1 to 7, comprising the steps of:

a) reacting at least one monomer A as defined in claim 1, 3 or 4 with at least one epoxide of formula III

